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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/056,343	04/07/1998	UFFE LOEBORG	3556.224-US	5207

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EXAMINER

MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/056,343	Applicant(s) LOEBORG, UFFE	
	Examiner William W. Moore	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 97-112 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 97-112 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

Applicant's Amendment filed January 16, 2004, canceling claims 77-96 in favor of the introduction of the new claims 97-112, has been entered and it is agreed that the new claims 97-104 overcome the rejection of record of claims herein under the first paragraph of 35 U.S.C. § 112. Although clauses (a) and (b) of the independent claim 97 remain incomplete, this issue is now treated herein under the second paragraph of the statute.

*Claim Rejections - 35 USC § 112***The following is a quotation of the first paragraph of 35 U.S.C. § 112:**

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 105-112 are rejected, essentially for reasons of record, under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is essentially the rejection of record where the new claim 105 differs from the claim it replaces, claim 87 subject to the rejection of record, in its preamble and in its clause (c) which now describe a selectable, less immunogenic, variant where the earlier claim 87 had described a method that screened DNA molecules encoding a selectable variant rather than a method of the new claim 105 that screens for a selectable variant. Yet the specification similarly fails to exemplify or describe the practice of the method of selection of the new claim 105, and the dependent claims 106-112 included in this rejection where they fail to introduce processes absent from claim 105, because the method set forth in claim 105 is not a method of selection that the specification

describes. While the specification exemplifies and describes methods of selection using antibodies, which may be monoclonal antibodies, conducted by separate incubations of antibodies raised to a reference protein with that reference protein as well as with one or more variants of the reference protein, as in Table IV of the specification, in parallel with separate incubations of antibodies raised to a variant protein with that variant protein, and other variant proteins, as well as with the reference protein, providing the multiple scores shown in Tables V and VI, the specification does not describe or exemplify the essentially subtractive procedure stated by claim 105. The skilled artisan in the relevant field of immunology would not have recognized the claimed process in a selection process the specification actually discloses. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). Thus the rejection of record is sustained.

Claims 97-112 are rejected under 35 U.S.C. § 112, first paragraph, because the specification is not enabling for a method of selecting a less immunogenic enzyme or medicinal protein by random alteration of the amino acid sequence or a reference proteins to produce selectable variants that may or may not be less immunogenic. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and use the invention commensurate in scope with these claims.

This is a new ground of rejection, based on a reconsideration of the scope of amino acid sequence alteration required where there is no resolution yet available of the tertiary structure of a generic reference enzyme or medicinal protein, such as was the case with subtilisins at the time the invention was made, facilitating Applicant's choice of amino acid sequence positions for manipulation. Claims 97-112 contemplate arbitrary assignments of any or all of amino acid substitutions, additions or deletions anywhere in the amino acid sequence of a generic enzyme or medicinal protein in a quest to identify epitopes, and then reduce or abolish the epitopes where, at most, its primary structure,

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i.e., its linear sequence of amino acids, may be determined with standard methods and without undue experimentation. This rejection is stated under the first paragraph of the statute because the specification cannot support the generation of variants of generic enzymes and medicinal proteins having a range of immunogenicity, yet retaining their enzymatic or medicinal activity, as a result of unlimited amino acid sequence alterations, where the alterations are amino acid insertions, deletions, or substitutions anywhere, in any combination or any pattern, made in the reference enzyme or medicinal protein. Indeed, neither the prior art made of record herewith nor Applicant's specification can, taken together, teach the selection of an unlimited numbers of amino acid positions for substitutions, additions, or deletions in a reference enzyme or medicinal protein in order to produce a range of immunogenicities in the resulting variants based solely on a knowledge of the primary sequence of a generic reference enzyme or medicinal protein, nor teach the nature of alterations that may be made which will permit a significant number of variants to retain their enzymatic or medicinal activity. Mere sequence perturbation cannot enable design and preparation of nucleotide sequences encoding a myriad of divergent enzymes or medicinal proteins that have any variation reducing the immunogenicity of any particular native epitope yet provide the public with a nucleotide sequence encoding a variant enzyme or medicinal protein that retains its native activity.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. § 112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying eight factors identified in *Ex parte Forman*, 230

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USPQ 546, 547 (Bd. Pat. App. & Int. 1986)). Applying the enablement analysis of

Wands, *supra*, to Applicant's disclosure, it is apparent that:

- a) the specification lacks adequate, specific, guidance for altering the amino acid sequences of generic enzymes and medicinal proteins to alter their immunogenicity to the extent recited in the claims without a resolution of their tertiary structure,
- b) the specification lacks working examples wherein any generic enzyme or medicinal proteins are altered to the extent required for successful practice of a claimed method, instead providing only a working example where the amino acid sequence of an subtilisin having a known tertiary structure is altered,
- c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,
- d) unpredictability exists in the art where no integral, generic, enzymes or medicinal proteins have been altered to the extent required for successful practice of a claimed method.

Thus the scope of methods jointly embraced by the phrases, "to produce one or more variants of the reference protein", and, "evoke[] a lower immunogenic response in an animal", is unsupported by the present specification for variants of generic enzymes and medicinal proteins that must retain the activity of the generic reference protein, even if taken in combination with teachings available in the prior art.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 97-112, are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following are several new grounds of rejection, some required by Applicant's Amendment filed January 16, 2004, and others, specifically the rejections of claims 98, 101, 106, and 109, rejections that might have been made previously. Claims 97 and 105 are rejected as indefinite because clauses (a) and (b) of these claims fail to provide a step for recombinantly producing, or isolating, reference proteins to which antibodies are raised, thus are incomplete. Claims 97 and 105 are further indefinite where clause (c) of claim 97 and clause (b) of claim 105 recite "mapping one or more epitopes . . .

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with immunological and proteochemical techniques” because the specification discloses only the mapping of epitopes by immunological techniques and fails to disclose, define, or discuss the nature of mapping by “proteochemical” techniques, thus the public and the artisan seeking to find the scope of the claims cannot determine the metes and bounds of the intended subject matter. Claims 98-104 and 106-112 are included in this aspect of the rejection because they fail to independently resolve the ambiguities of claims 97 and 105 from which they depend.

Claims 98 and 106 are indefinite in reciting the term “industrial enzyme” because the specification fails to disclose, define, or discuss the nature of what is, and what is not, an industrial enzyme and any enzyme that functions in nature can be put to some use in industry, thus the public and the artisan seeking to find the scope of the claims cannot determine the metes and bounds of the intended subject matter.

Claims 101 and 109 are indefinite in reciting the term “process enzyme” because the specification fails to disclose, define, or discuss the nature of what is, and what is not, a process enzyme, and all enzymes functioning in nature do so as part of biological or physiological processes, thus the public and the artisan seeking to find the scope of the claims cannot determine the metes and bounds of the intended subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 97-112 remain rejected, essentially for reasons of record, under 35 U.S.C. § 103(a) as being unpatentable over Ladner et al., U.S. 5,223,409, of record.

Applicant's arguments filed January 16, 2004, have been fully considered with respect to the new claims 97-112, but they are not persuasive where Applicant argues limitations absent from the claims. The new claims do not describe methods requiring epitope mapping of integral enzymes or medicinal proteins, in accord with Applicant's arguments, thus do not avoid the teachings of Ladner et al., particularly where medicinal proteins may be quite small, e.g. peptide hormones, and Ladner et al. teach the modification of the amino acid sequence of a medicinal protein, which is also an enzyme, streptokinase, that is "antigenic to an undesirable extent" to produce a variant polypeptide with reduced allergenicity. Clauses (a) and (b) of claim 97 and clauses (a)-(c) of claim 105 still fail to differentiate a claimed method from that of Ladner et al. because, like Ladner et al., the new claims do not require the mapping, *a priori*, of a specific antigenic epitope, and then its reduction, but state a generalized screening procedure. Ladner et al. therefore remains prior art under 35 U.S.C. §103(a) where it is clear from the teachings of Ladner et al. that they were aware that antigenic epitopes were present in the structure of streptokinase and also aware that their processes, comprising preparation of DNA molecules encoding variants of the reference streptokinase polypeptide, would identify regions that contribute to antigenicity, i.e., epitopes, and reduce the antigenicity of streptokinase, thus achieving the same result indicated in the closing phrases of the final clauses of methods of claims 77 and 78. Where there is no cognizable distinction between a native enzyme and any "industrial" enzymes or "process" enzymes, as explained above, claims 98, 101, 106, and 109 are included in this rejection which is sustained with respect to the new claims 97-112.

Conclusion

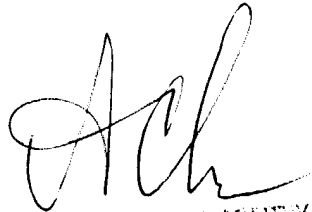
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

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more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can now be reached at 571.272.0928. The fax phone numbers for all communications for the organization where this application or proceeding is assigned remains 703.872.9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is now 571.272.1600.

William W. Moore
June 25, 2004


PONNATHAPURA ACHUTAMURTHY
SUPERVISOR/ART UNIT 1652/SSW
TELEPHONE/AVOIDANCE 1600